UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 22-11546-RGS

RADIUS HEALTH, INC.
and IPSEN PHARMA S.A.S.

v.

ORBICULAR PHARMACEUTICAL
TECHNOLOGIES PRIVATE LIMITED

FINDINGS OF FACT, RULINGS OF LAW, AND ORDER AFTER A BENCH TRIAL

July 30, 2025

STEARNS, D.J.

In September of 2022, plaintiffs Radius Health, Inc. (Radius), and Ipsen Pharma S.A.S. (Ipsen) filed this patent infringement action against defendant Orbicular Pharmaceutical Technologies Private Limited (Orbicular) based on its filing of an Abbreviated New Drug Application (ANDA) to market a generic version of Radius's Tymlos product. Although plaintiffs initially asserted several claims of United States Patent Nos. 8,748,382 (the '382 patent), 8,148,333 (the '333 patent), RE49,444 (the '444 patent), 10,996,208 (the '208 patent), and 11,782,041 (the '041 patent) (collectively, the Asserted Patents), by the time of trial, only the following claims remained in dispute: claim 7 of the '382 patent; claims 2, 11, and 13 of

the ’333 patent; claims 20, 34, and 57 of the ’444 patent; claims 14 and 15 of the ’208 patent; and claims 6 and 12 of the ’041 patent.

The court convened a ten-day bench trial between March 17, 2025, and April 2, 2025. The issues to be tried included (1) whether claim 7 of the ’382 patent; claims 2, 11, and 13 of the ’333 patent; and claims 20, 34, and 57 of the ’444 patent are invalid as obvious; and (2) whether claims 14 and 15 of the ’208 patent; and claims 6 and 12 of the ’041 patent are invalid as not enabled or lacking adequate written description.[1] Based on the credible testimony and exhibits offered at trial, the court makes the following findings and rulings.[2]

FACTUAL FINDINGS

The Parties

1. Radius is a Massachusetts corporation with its principal place of business at 22 Boston Wharf Road, 7th Floor, Boston, Massachusetts 02210. Joint Pretrial Statement (JPS) [Dkt # 219] ¶ 1.

[1] Orbicular has stipulated that marketing its proposed generic would infringe these claims. *See* JPS ¶ 52.

[2] Following the trial, the parties were invited to submit proposed findings of fact and rulings of law, which they did, and from which the court has benefitted.

2. Ipsen is a French limited company with its principal place of business at 65 Quai George Gorse, 92100 Boulogne-Billancourt, France. JPS ¶ 2.

3. Orbicular is an Indian business entity with a principal place of business at P. No. 53, ALEAP Industrial Estate, Behind Pragati Nagar Kukatpally, Hyderabad, 500 090 Telangana, India. JPS ¶ 3.

Peptides

4. A peptide is a protein with roughly 50 or less amino acids in its chain. Karpf Test., Day 1 Tr. [Dkt # 273] at 70.

5. Peptides generally have two types of structure: primary and secondary. Trout Test., Day 7 Tr. [Dkt # 269] at 853;[3] Forrest Test., Day 3 Tr. [Dkt # 275] at 311, 313. Primary structure refers to the sequence of amino acids in the peptide. Trout Test., Day 7 Tr. at 853. Secondary structure refers to the three-dimensional arrangement of the peptide when the individual amino acids in the sequence interact to form motifs such as alpha helices. *Id.* at 853-854.

[3] Despite conceding his expertise prior to trial, Orbicular bafflingly attempted to impeach Dr. Trout during cross-examination based on the contents of his 1996 Ph.D. thesis and an out-of-context statement he made in a different case more than 20 years ago. As it intimated during trial, the court does not find such stale evidence persuasive in discrediting Dr. Trout's otherwise credible testimony.

6. Peptides, like all pharmaceutical ingredients, eventually degrade. Forrest Test., Day 3 Tr. at 313; Trout Test., Day 7 Tr. at 851. Three common types of degradation are oxidation;[4] deamidation;[5] and isomerization.[6] Forrest Test., Day 2 Tr. [Dkt # 274] at 234-237.

7. Peptide stability is the resistance of a peptide towards various routes of degradation. Trout Test., Day 7 Tr. at 851.

Drug Development

General

8. Drug development begins with nonclinical animal studies to determine the pharmacology of the peptide (called the active pharmaceutical ingredient, or API) and the levels at which adverse events may occur. Karpf Test., Day 1 Tr. at 54.

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[4] Oxidation occurs when one or more oxygen atoms are added to a site within a peptide. Trout Test, Day 8 Tr. [Dkt # 270] at 863. Methionine is particularly susceptible to oxidation. Forrest Test., Day 3 Tr. at 234, 255.

[5] Deamidation occurs when a nitrogen atom in the amide group side chain of glutamine or asparagine is substituted with an oxygen atom, creating a new amino acid. Forrest Test., Day 2 Tr. at 234-235; Trout Test, Day 8 Tr. at 864.

[6] Isomerization occurs when the atoms in a peptide rearrange into a different configuration, causing the peptide to have different chemical and physical properties. Prestwich Test., Day 5 Tr. [Dkt # 267] at 485-486; *see also* Forrest Test., Day 2 Tr. at 236-237.

9. The next step is to file an Investigational New Drug (IND) application with the Food and Drug Administration (FDA) disclosing the results of nonclinical testing. *Id.* at 94. The FDA must approve the IND before any testing is performed on humans. *Id.*

10. Clinical (*i.e.*, human) testing proceeds in three phases. *Id.* at 54.

11. In Phase I, healthy volunteers take ascending doses of the drug. *Id.* at 54-55. They begin with a very low dose, then increase the dose over time until they reach a dose that causes dosage limiting toxicity. *Id.*

12. In Phase II, the middle two to four dosages from the Phase I trials are tested in patients with the relevant condition. *Id.* at 56.

13. Phase III is the pivotal stage in terms of ultimate approval from the FDA. *Id.* at 57. Researchers take the most effective dosage from the Phase II trials and perform additional testing to determine if administration of the drug leads to a clinically meaningful endpoint – in other words, whether the drug is effective in treating the condition. *Id.* at 57-58.

14. Most drugs fail during the development process. Leder Test., Day 7 Tr. at 731; *see also* Trial Ex. 48. Only five of the twenty-three drug products on which Dr. Karpf has worked, for example, have reached final FDA approval, and he considers this to be a good success rate. Karpf Test.,

Day 1 Tr. at 127; *see also id.* (noting that few others in the drug development industry have had five drugs approved).

Formulation Science

15. Peptides cannot be administered on their own to human patients. Karpf Test., Day 2 Tr. at 206; Trout Test., Day 8 Tr. at 861. They must be formulated with inactive ingredients (excipients) into a pharmaceutical product for administration. Karpf Test., Day 2 Tr. at 206; Forrest Test., Day 2 Tr. at 210; Trout Test., Day 8 Tr. at 861.

16. Common excipients include buffers, preservatives, and stabilizers. A buffer acts like a sponge, releasing and absorbing excess protons to maintain a given pH. Forrest Test., Day 3 Tr. at 268. A preservative works as an anti-microbial agent to maintain sterility. *Id.* at 274. A stabilizer protects against certain types of degradation processes. Trout Test., Day 8 Tr. at 882.

17. There are tools available to help formulators choose which excipients to use in a composition. Trout Test., Day 8 Tr. at 871; *see also, e.g.*, Trial Ex. FU at 2. *The Handbook of Pharmaceutical Excipients* (*The Handbook*), for example, provides "information about the properties and uses of" certain commonly used excipients. Forrest Test., Day 3 Tr. at 270.

18. These tools do not, however, necessarily render formulation routine. Excipients may, for example, have unintended effects in a composition. Trout Test., Day 8 Tr. at 876. "[T]he majority of protein formulation research and development requires a great amount of trial and error to finalize the type and amount of formulation components." Trial Ex. EE at 53.

19. The first step in developing a stable formulation for any peptide is to determine the routes of degradation for that peptide. Forrest Test., Day 23 Tr. at 252-253; Trial Ex. FU at 2.

20. pH[7] impacts all major degradation pathways. Trial Ex. FU at 5. The ideal pH to minimize deamidation, for example, is generally between 4 and 5. Forrest Test., Day 3 Tr. at 256. And the ideal pH to minimize isomerization would generally be above 6, although even at a pH of 5, isomerization begins to fall. *Id.* at 261-262.

Osteoporosis

21. Most humans, once they reach their adult height, undergo a process called bone remodeling. Karpf Test., Day 1 Tr. at 62; Leder Test.,

[7] pH is the measure of the acidity of a solution. Trout Test., Day 8 Tr. at 867. The physiological pH of humans is generally about 7.4. Forrest Test., Day 2 Tr. at 240. The ideal pH for a drug product thus is 7.4 in terms of tolerability. Forrest Test., Day 3 Tr. at 241. Formulators usually depart from this baseline, however, for reasons of stability and solubility. *Id.*

Day 6 Tr. [Dkt # 268] at 695. During bone remodeling, bone reabsorbing cells (osteoclasts) remove a pocket of old bone, creating a cavity which is then filled with new bone by bone forming cells (osteoblasts). Karpf Test., Day 1 Tr. at 63-64; Leder Test., Day 6 Tr. at 695.

22. In healthy humans, the amount of old bone removed is generally the same as the amount of new bone created. Karpf Test., Day 1 Tr. at 64. When the processes are not evenly matched, however, osteoporosis occurs. *Id.* at 64-65; Leder Test., Day 6 Tr. at 695.

23. Osteoporosis is a systemic condition characterized by decreased bone mass and impaired bone quality, which together decrease the strength of bone and increase the risk of fractures. Karpf Test., Day 1 Tr. at 60; *see also* Leder Test., Day 6 Tr. at 694.

24. There are two classes of drugs available to treat this condition: (1) antiresorptive drugs, which work by decreasing osteoclast bone resorption; and (2) anabolic drugs, which work by increasing osteoblast bone formation. Karpf Test., Day 1 Tr. at 71, 73; Leder Test., Day 6 Tr. at 700-701.

25. Antiresorptive drugs can pose a safety risk if used over the long term. Karpf Test., Day 1 Tr. at 72-73; Leder Test., Day 6 Tr. at 702. If you over-suppress bone turnover, for example, it can, in rare cases, induce side effects like osteoporosis of the jaw or an unusual type of hip fracture. Karpf

Test., Day 1 Tr. at 73. Antiresorptives also lose efficacy over time. Leder Test., Day 6 Tr. at 702.

26. As of the priority date of the '382, '333, and '444 patents, Forteo was the only anabolic drug approved by the FDA. Karpf Test., Day 2 Tr. at 145-146; Leder Test., Day 6 Tr. at 702. Forteo comes in the form of a prefilled multidose injection pen. Trial Ex. 37.

27. The API in Forteo, teriparatide, is a fragment of parathyroid hormone (PTH). Karpf Test., Day 1 Tr. at 73; Leder Test. Day 6 Tr. at 703.

28. PTH is a hormone produced by the parathyroid gland which helps control the calcium level in blood. Karpf Test., Day 1 Tr. at 51; Leder Test., Day 6 Tr. at 703. In its natural form, PTH consists of 84 amino acids. Karpf Test., Day 1 Tr. at 73; Leder Test., Day 6 Tr. at 695; *see also* Forrest Test., Day 3 Tr. at 317.

29. Teriparatide is the first 34 amino acids of PTH. Karpf Test., Day 1 Tr. at 73; Leder Test., Day 6 Tr. at 703.

30. Forteo is not storage-stable at room temperature; it needs to be refrigerated between uses. Leder Test., Day 6 Tr. at 704; Karpf Test., Day 1 Tr. at 81. The need for refrigeration can have a negative impact on patient adherence to treatment. Leder Test., Day 6 Tr. at 705; *see also* Karpf Test.,

Day 2 Tr. at 148 (acknowledging that some patients find it difficult to travel with Forteo).

The Development of Tymlos

31. In the 1990s, Ipsen discovered the peptide abaloparatide, a synthetic analog of the first 34 amino acids of parathyroid hormone related protein (PTHrP). Karpf Test., Day 1 Tr. at 74; Forrest Test., Day 3 Tr. at 319-320; Shah Test., Day 6 Tr. at 616. PTHrP is a naturally occurring protein closely related to PTH. Karpf Test., Day 1 Tr. at 74. It interacts with the same receptor as PTH and forms essentially the same three-dimensional shape. *Id.* 74.

32. The chemical sequence for abaloparatide is Ala-Val-Ser-Glu-His-Gln-Leu-Leu-His-Asp-Lys-Gly-Lys-Ser-Ile-Gln-Asp-Leu-Arg-Arg-Arg-Glu-Leu-Leu-Glu-Lys-Leu-Leu-Aib-Lys-Leu-His-Thr-Ala-NH2. JPS ¶ 7. This sequence was first disclosed to the public in 1997. Trout Test., Day 8 Tr. at 887.

33. Ipsen filed for patent protection on the abaloparatide peptide on September 20, 1999. U.S. Patent No. 6,544,949 (the '949 patent) [Trial Ex. EC], covering a method of treating osteoporosis with abaloparatide, issued on April 8, 2003. *See* '949 patent; *see also* Karpf Test., Day 1 Tr. at 100-101.

34. The ’949 patent expired before the commencement of this lawsuit. Karpf Test., Day 1 Tr. at 115.

35. Ipsen ran into technical challenges related to impurity levels and stability while attempting to formulate abaloparatide into a drug product. Shah Test., Day 6 Tr. at 618.

36. In 2005, after several years of unsuccessful effort on its own, Ipsen licensed the rights to abaloparatide to Radius to co-develop a drug product. *Id.* at 617-618.

37. Radius and Ipsen worked together to develop an abaloparatide formulation that would be storage stable and safe for administration to humans. *Id.* at 618-619. The claims of the ’382, ’333, and ’444 patent are directed to this formulation.

38. During the final stages of development, Radius and Ipsen detected a previously unidentified degradation in its drug product which caused the peptide to become less effective. *See* Trial Ex. 77; *see also* Pentelute Test., Day 10 Tr. [Dkt # 271] 1096-1097. The degradation, which Radius termed beta-Asp10, was an isomerization of the aspartic acid at position 10. See Trial Ex. 77; Prestwich Test., Day 5 Tr. at 488; Pentelute Test., Day 10 Tr. at 1097.

39. The ’208 and ’041 patents are directed to formulated abaloparatide drug products containing less than a certain threshold of the beta-Asp10 impurity.

40. The FDA approved Radius’ and Ipsen’s drug product – a prefilled multi-dose pen containing daily doses of 80 μg of abaloparatide – for the treatment of osteoporosis on April 28, 2017. JPS ¶¶ 4-5, 8-9. Radius began selling that product, which it named Tymlos, shortly thereafter. *Id.* ¶ 10.

41. Unlike Forteo, Tymlos is stable at room temperature and does not need to be refrigerated between uses. Karpf Test., Day 1 Tr. at 81; Karpf Test., Day 2 Tr. at 148; Leder Test., Day 7 Tr. at 726; *see also* Shah Test., Day 6 Tr. at 648-649.

42. The FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” publication (the Orange Book) lists the Asserted Patents in the entry for Tymlos. JPS ¶ 46.

The Asserted Patents

43. The ’382 patent is entitled “Method of drug delivery for bone anabolic protein,” and issued on June 10, 2014.

44. The priority date for the ’382 patent is October 3, 2006, which is the date U.S. Provisional Application No. 60/848,960 was filed.

45. Asserted claim 7 of the '382 patent depends from claims 6, 5, and 1. Claims 7, 6, 5, and 1 recite:

> **7.** The method of claim 6, wherein said pH buffer is an acetate buffer.
>
> **6.** The method of claim 5, wherein said storage-stable composition further comprises phenol in a concentration from about 0.25 to about 5 mg/mL.
>
> **5.** The method of claim 1, wherein said subject is administered the storage stable composition by subcutaneous injection of an amount of said composition containing from about 75 to about 80 μg of [$Glu^{22,25}$, $Leu^{23,28,31}$, Aib^{29}, $Lys^{26,30}$] hPTHrP(1-34)NH2(SEQ ID NO.2).
>
> **1.** A method of stimulating bone growth in a subject in need thereof comprising administering to said subject a storage stable composition comprising:
>
> a) a PTHrP having the sequence [$Glu^{22,25}$, $Leu^{23,28,31}$, Aib^{29}, $Lys^{26,30}$] hPTHrP(1-34)NH2 (SEQ ID NO.2); and
>
> b) an effective amount of buffer to maintain the pH in a range of about 4.5 to about 5.6.

The '333 Patent

46. The '333 patent is entitled "Stable composition comprising a PTHrP analogue," and issued on April 3, 2012.

47. The priority date for the '333 patent is October 3, 2006, which is the date U.S. Provisional Application No. 60/848,960 was filed.

48. Asserted claim 2 of the '333 patent depends from claim 1. Claims 2 and 1 recite:

> **2.** The storage-stable composition according to claim 1, wherein said pH is about 5.1.
>
> **1.** A storage-stable composition suitable for administration to a subject comprising:
>
> a) a PTHrP analogue having the sequence [Glu^{22,25}, Leu^{23,28,31}, Aib^{29}, Lys^{26,30}] hPTHrP(1-34)NH2(SEQ ID NO.2); and
>
> b) an effective amount of a pH buffer to maintain the pH in a range of about 4.5 to about 5.6.

49. Asserted claim 11 of the '333 patent depends from claims 10, 9, 8, and 1. Claims 11, 10, 9, and 8 recite:

> **11.** The storage-stable composition according to claim 10, wherein said phenol is present in a concentration of about 5 mg/mL.
>
> **10.** The storage-stable composition according to claim 9, wherein said phenol is present in a concentration from about 0.25 to about 5 mg/mL.
>
> **9**. The storage-stable composition according to claim 8, wherein said anti-microbial agent is phenol.
>
> **8.** The storage-stable composition according to claim 1, further comprising an effective amount of an anti-microbial agent.

50. Asserted claim 13 of the '333 patent depends from claim 1. Claim 13 recites:

> **13.** The storage-stable composition according to claim 1, wherein said composition does not contain a chemical stabilizer.

The '444 Patent

51. The '444 patent is entitled "Method of treating osteoporosis comprising administration of PTHrP analog," and issued on March 7, 2023.

52. The '444 patent is a reissue of U.S. Patent No. 7,803,770, which was issued on September 28, 2010.

53. The priority date for the '444 patent is October 3, 2006, which is the date U.S. Provisional Application No. 60/848,960 was filed.

54. Asserted claim 20 of the '444 patent depends from claims 19, 18, 17, and 16. Claims 20, 19, 18, 17, and 16 recite:

> **20.** The method according to claim 19, wherein the composition comprises 5 mg/mL phenol.
>
> **19.** The method according to claim 18, wherein the anti-microbial agent is phenol.
>
> **18.** The method according to claim 17, wherein the anti-microbial agent is selected from phenol, chlorocresol, and methylparaben/propylparaben, or a combination thereof.
>
> **17.** The method according to claim 16, wherein the composition further comprises an anti-microbial agent.
>
> **16.** A method of treating osteoporosis comprising daily subcutaneous administration of a composition comprising 80 µg of [Glu^{22,25}, Leu^{23,28,31}, Aib^{29}, Lys^{26,30}]hPTHrP(1-34)NH2 to a human in need thereof, wherein the composition is delivered in a multi-dose injection pen.

55. Asserted claim 34 of the '444 patent depends from claims 31, 28, 25, 22, 21, and 17 or 16. Claims 34, 31, 28, 25, 22, and 21 recite:

> **34.** The method according to claim 31, wherein the sodium acetate is sodium acetate trihydrate.
>
> **31.** The method according to claim 28, wherein the acetate buffer comprises acetic acid and sodium acetate.
>
> **28.** The method according to claim 25, wherein the buffer is an acetate buffer.
>
> **25.** The method according to claim 22, wherein the buffer is selected from a citrate buffer and an acetate buffer, or a combination thereof
>
> **22.** The method according to claim 21, wherein the composition comprises a buffer in an amount effective to maintain the pH at about 5.1.
>
> **21.** The method according to claim 16 or claim 17, wherein the composition further comprises a buffer.

56. Asserted claim 57 of the '444 patent depends from claims 54 and 16. Claims 57 and 54 recite:

> **57.** The method according to claim 54, wherein the concentration of [Glu^{22,25}, Leu^{23,28,31}, Aib^{29}, Lys^{26,30}]hPTHrP(1-34)NH2 in the composition is at least 98.9% of its initial concentration at t=0 after 1 month at 25° C.
>
> **54.** The method according to claim 16, wherein the concentration of [Glu^{22,25}, Leu^{23,28,31}, Aib^{29}, Lys^{26,30}]hPTHrP(1-34)NH2 in the composition is at least 98.9% of its initial concentration at t=0 after 1 month.

The ’208 Patent

57. The ’208 patent is entitled “Abaloparatide formulations and methods of testing, storing, modifying, and using same” and issued on May 4, 2021.

58. The priority date for the ’208 patent is April 28, 2017, which is the date U.S. Provisional Application No. 62/492,022 was filed.

59. Asserted claims 14 and 15 of the ’208 patent recite:

> **14.** A formulated abaloparatide drug product comprising ≤5% w/w beta-Asp10 of the total peptide content, and an aqueous buffer having a pH from 4.5-5.5, wherein said formulated abaloparatide drug product has an abaloparatide concentration of between 1.8 mg/mL and 2.2 mg/mL, wherein the suitability of the formulated abaloparatide drug product for administration to a subject has been established by a method comprising: detecting and quantifying the presence of ≤5% w/w beta-Asp10 of the total peptide content in the formulated abaloparatide drug product.
>
> **15.** The formulated abaloparatide drug product of claim 14, comprising ≤1.0% w/w beta-Asp10 of the total peptide content.

The ’041 Patent

60. Asserted claim 6 of the ’041 patent depends from claims 4 and 3, 2, or 1. Claims 6, 4, 3, 2, and 1 of the ’041 patent recite as follows:

> **6.** The method according to claim 4, wherein a multi-dose injection pen is used to administer the drug over a period of up to 30 days.

> **4.** A method of treating a subject in need thereof, the method comprising administering to the subject in need thereof the formulated abaloparatide drug product according to any one of claims 1 to 3, at a daily dosage of about 80 µg of abaloparatide.
>
> **3.** The formulated abaloparatide drug product of claim 1, wherein the formulated abaloparatide drug product comprises ≤0.5% w/w of betaAsp10, based on a total peptide content of the formulated abaloparatide drug product.
>
> **2.** The formulated abaloparatide drug product of claim 1, wherein the formulated abaloparatide drug product comprises ≤1% w/w of beta-Asp10, based on a total peptide content of the formulated abaloparatide drug product.
>
> **1.** A formulated abaloparatide drug product comprising an aqueous buffer, wherein said formulated abaloparatide drug product has an abaloparatide concentration of between 1.8 mg/mL and 2.2 mg/mL, wherein said formulated abaloparatide drug product has a pH from 4.5-5.5, and wherein said formulated abaloparatide drug product comprises ≤3% w/w of beta-Asp10, based on a total peptide content of the formulated abaloparatide drug product.

61. Asserted claim 12 of the ’041 patent depends from claims 11, 10, and 9, 8, or 7. Claims 12, 11, 10, 9, 8, and 7 recite:

> **12.** The method according to claim 11, wherein a multi-dose injection pen is used to administer the drug over a period of up to 30 days.
>
> **11.** The method according to claim 10, wherein the administration is subcutaneous.
>
> **10.** A method of treating a subject in need thereof, the method comprising administering to the subject in need

> thereof the formulated abaloparatide drug product according to any one of claims 7 to 9, at a daily dosage of about 80 μg of abaloparatide.
>
> **9.** The formulated abaloparatide drug product of claim 7, wherein the formulated abaloparatide drug product comprises between 0.1% and ≤5% w/w beta-Asp10, based on a total peptide content of the formulated abaloparatide drug product.
>
> **8.** The formulated abaloparatide drug product of claim 7, wherein the formulated abaloparatide drug product comprises between 0.01% and ≤5% w/w beta-Asp10, based on a total peptide content of the formulated abaloparatide drug product.
>
> **7.** A formulated abaloparatide drug product comprising an aqueous buffer, wherein said formulated abaloparatide drug product has an abaloparatide concentration of between 1.8 mg/mL and 2.2 mg/mL, wherein said formulated abaloparatide drug product has a pH from 4.5-5.5, and wherein said formulated abaloparatide drug product comprises between 0% to ≤5% w/w of beta-Asp10, based on a total peptide content of the formulated abaloparatide drug product.

Orbicular's ANDA

62. On June 21, 2022, Orbicular filed ANDA No. 217245, seeking to market and sell a generic version of Tymlos prior to the expiration date of the Asserted Patents. JPS ¶¶ 11-12.

63. ANDA No. 218245 contains a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (Paragraph IV Certification) that, to the best of

Orbicular's knowledge, each of the Asserted Patents is invalid or will not be infringed by the manufacture, use, or sale of the proposed generic. JPS ¶ 47.

64. On August 9, 2022, Radius and Ipsen received a notice letter from Orbicular regarding its Paragraph IV Certification.[8] JPS ¶ 48.

65. Radius and Ipsen filed this case 42 days later, on September 20, 2022. JPS ¶ 50.

66. Because plaintiffs sued Orbicular within 45 days of receiving Orbicular's notice letter, they became entitled to a 30-month stay of regulatory approval of the ANDA. This stay expired on February 9, 2025. JPS ¶ 51.

67. Orbicular's ANDA product has not yet received FDA approval. JPS ¶ 13. In internal documents, Orbicular referred to abaloparatide as "[h]ighly complex" and "inherently unstable." Trial Ex. DB.

Person of Ordinary Skill in the Art

68. A person of ordinary skill in the art (POSA) for the asserted claims of the '444 and '382 patents as of the October 3, 2006 priority date would have been an individual or team including (1) an organic chemist with

[8] The '444 patent and '041 patent issued after the commencement of this lawsuit. Orbicular's 2022 notice letter accordingly only referenced the '382 patent, '333 patent, and '216 patent. JPS ¶ 48. Orbicular sent notice regarding the '444 patent and '041 patent on April 16, 2024. JPS ¶ 49.

experience in synthesizing and analyzing peptides; (2) a medical doctor who is an expert in osteoporosis and has experience in clinical drug development; and (3) a pharmaceutical formulator with experience in formulating peptides for injection.

69. Drs. Karpf, Forrest, Leder, and Trout qualify as POSAs under this definition.[9]

70. A POSA for the asserted claims of the '333 patent as of the October 3, 2006 priority date would have been an individual or team including (1) an organic chemist with experience in synthesizing and analyzing peptides; (2) a medical doctor who is an expert in osteoporosis; and (3) a pharmaceutical formulator who has several years' experience formulating peptides for injection and an advanced degree such as a Masters, Ph.D., or equivalent in pharmaceutics, chemistry, chemical engineering or a related field.

71. Drs. Forrest and Trout qualify as POSAs under this definition.

72. A POSA for the asserted claims of the '208 and '041 patents would have been an individual with a graduate-level degree (*i.e.*, a master's

[9] The court rejects the contention that Dr. Leder lacks the requisite clinical drug development experience because he has not designed a Phase I study. He has reviewed the results of Phase I studies and has designed and carried out clinical trials in the other phases of development. Leder Test, Day 6 Tr. at 682-683.

degree or higher) in the field of chemistry, including relevant coursework in organic chemistry, analytical chemistry, peptide science; or a bachelor's degree with equivalent industry experience working with peptides.

73. Drs. Penteluete and Prestwich qualify as POSAs under this definition.

Asserted Prior Art References

74. Orbicular asserts that claim 7 of the '382 patent; claims 2, 11, and 13 of the '333 patent; and claims 20, 34, and 57 of the '444 patent are obvious in view of various combinations of the following references.

The '949 Patent

75. The '949 patent is directed to a method of treating osteoporosis using abaloparatide. '949 patent, cl. 1. The patent does not disclose any in vitro data from testing abaloparatide, nor does it disclose any specific formulation or dosing regimen. Karpf Test, Day 2 Tr. at 159, 161-162; Forrest Test., Day 4 Tr. [Dkt # 291] at 409.

Dong 2001

76. Dong 2001 [Trial Ex. EG] is an abstract from a conference of the American Peptide Society. Trout Test., Day 8 Tr. at 897. It was not peer reviewed. Karpf Test., Day 2 Tr. at 179.

77. Dong 2001 begins by noting that PTH and teriparatide, although effective in increasing bone mass in animals and humans, have a relatively narrow therapeutic window given concerns of bone resorption and hypercalcemia. Dong 2001 at 1. It purports to address this issue by identifying eight PTHrP analogs that may have a wider therapeutic index. *Id.* One of the eight analogs is abaloparatide. *Id.*

78. Dong 2001 summarizes the results of three nonclinical animal studies performed by Ipsen. *Id.* at 2. According to Dong 2001, these studies demonstrate that abaloparatide has a lower tendency to mobilize calcium than PTH, which would contribute to a wider therapeutic index, and was twice as effective. *Id*; Karpf Test., Day 1 Tr. at 103.

79. Dong 2001 does not identify the formulation or dose concentration used in any of the Ipsen studies. Karpf Test., Day 2 Tr. at 182.

80. In a communication with Radius in 2008, Dr. Karpf expressed doubt that the results from the Ipsen studies were clinically meaningful. Trial Ex. AJ. For example, he noted that the true potency differential between abaloparatide and teriparatide/PTH was likely less than twofold because (1) the underlying studies were performed on rats, and rat studies are less predictive than monkey studies; and (2) the studies did not include

a control of teriparatide up to the full amount of abaloparatide administered, even though teriparatide is more effective at higher doses. *Id.*

International Patent Application No. WO96/40775

81. International Patent Application No. WO96/40775 (WO '775) [Trial Ex. EO] discusses improving the efficacy of drugs by modifying the last half of a molecule. Karpf Test., Day 1 Tr. at 107; Karpf Test., Day 2 Tr. at 163. It does not, however, provide any clinical data, nor does it mention abaloparatide (which had not yet been discovered). Leder Test., Day 7 Tr. at 755-756; Karpf Test., Day 2 Tr. at 163.

82. Compound I in WO '775 contains 33 amino acids in common with abaloparatide. Karpf Test., Day 1 Tr. at 89. The only difference is that Compound I has a glutamic acid at position 29, while abaloparatide has non-natural aminoisobutyric acid (AiB) at position 29. *Id.*; Forrest Test., Day 4 Tr. at 431; Trout Test., Day 7 Tr. at 850.

83. Even changing just one amino acid, however, creates a different peptide with pharmacological properties. Trout Test., Day 7 Tr. at 850.

Forteo Label

84. As previously discussed, Forteo is a prefilled multidose injection pen for the treatment of osteoporosis. The API in Forteo is teriparatide, a fragment of PTH comprising the first 34 amino acids of its sequence.

85. The Forteo label [Trial Ex. 37] discloses that the developer tested teriparatide at doses of both 20 μg and 40 μg during Phase III trials. Although the label reports that adverse events associated with either dose were mild and generally did not require discontinuation of therapy, Forteo is only approved by the FDA at a dose of 20 μg.[10]

U.S. Patent Publication No. 2002/0107200 (the '200 publication)

86. U.S. Patent Publication No. 2002/0107200 (the '200 publication) [Trial Ex. ED] is directed to a stabilized pharmaceutical composition for administering teriparatide. The composition uses a buffer (preferably acetate), stabilizer (preferably mannitol), and anti-microbial preservative (preferably m-cresol), and the preferred pH range is 3 to 6. '200 publication, ¶ 30.

U.S. Patent No. 6,583,114 (the '114 patent)

87. U.S. Patent No. 6,583,114 (the '114 patent) [Trial Ex. EB] is directed to healing bone and repairing fractures using PTHrP analogs. It notes that various natural and non-natural amino acids may be used to create

[10] A publication summarizing the results of the Phase III trials explains why the dosage of 20 μg was chosen – although subjects in the 40 μg dosage group experienced a higher increase in bone mineral density than those in the 20 μg dosage group, the two groups had similar rates of reduction in fracture (the ultimate clinical endpoint), and subjects in the 40 μg dose were more likely to have more side effects than the those in the 20 μg dosage group. Trial Ex. 36 at 1.

a PTHrP analog, and it provides examples of roughly thirty of those non-natural amino acids. '114 patent, col. 3, ll. 33-54. It does not, however explain which specific amino acids from this list should be used and when/where substitutions should be made. Forrest Test., Day 3 Tr. at 330; Trout Test, Day 8 Tr. at 916.

88. The '114 patent does not disclose the sequence for abaloparatide. Forrest Test., Day 3 Tr. at 330-331.

89. Among other formulations addressed to other methods of administration (*e.g.*, capsule or nasal), the '114 patent discloses a generic injectable formulation containing an unspecified "compound of this invention," sodium acetate as a buffer, and no stabilizer.[11] '114 patent, col. 13, ll. 31-42. It does not identify a specific pH for the composition. Trout Test, Day 8 Tr. at 917.

The Handbook Entries

90. *The Handbook* contains entries for several excipients, including the buffer sodium acetate and the preservative phenol. The entries describe at a high level the properties of these excipients, how they are manufactured, safety and handling concerns, and regulatory status. Trial Exs. EL, EM.

[11] Other, more tangible injectable formulations described in the specification do, however, use stabilizers. *See id.*, col. 15, l. 31-col. 16, l. 20.

RULINGS OF LAW

91. Patents are presumed valid. 35 U.S.C. § 282(a). Orbicular, as the party challenging the Asserted Patents, bears the burden of establishing invalidity by "clear and convincing evidence." *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011); *see also* § 282(a).

Obviousness

92. "Under the U.S. Patent Act, an invention cannot be patented if 'the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009), quoting 35 U.S.C. § 103.

93. Obviousness is a question of law based on the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). These factors include: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations, such as commercial success, long felt but unsolved need, or failure of others. *Id.* at 17-18; *see also Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1327 (Fed. Cir. 2017) ("Obviousness is a mixed question of fact and law.").

94. "The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008). Thus, a "patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The party seeking invalidation must further demonstrate "that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007).

95. A reasonable expectation of success will not be defeated "simply by a showing of some degree of unpredictability in the art." *Id.* at 1364. "[T]he expectation of success need only be reasonable, not absolute." *Id.*

Enablement

96. "The first paragraph of 35 U.S.C. § 112 requires that the specification of a patent must enable a person skilled in the art to make and use the claimed invention." *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988). Enablement is a question of law based on underlying factual findings. *Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1281 (Fed. Cir. 2007).

97. "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co.*, 308 F.3d 1167, 1185 (Fed. Cir. 2002), quoting *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 858 F.2d at 737, quoting *In re Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982).

98. "Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d at 737.

Written Description

99. Section 112 "contains a written description requirement separate from enablement." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336,

1351 (Fed. Cir. 2010). The written description requirement "provides, in pertinent part, that '[t]he specification shall contain a written description of the invention.'" *Nuvo Pharms. (Ireland) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc.*, 923 F.3d 1368, 1376 (Fed. Cir. 2019), quoting 35 U.S.C. § 112.

100. "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms.*, 598 F.3d at 1351.

101. "The essence of the written description requirement is that a patent applicant, as part of the bargain with the public, must describe his or her invention so that the public will know what it is and that he or she has truly made the claimed invention." *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1298 (Fed. Cir. 2014).

ULTIMATE FINDINGS OF FACT AND RULINGS OF LAW

Obviousness

Claim 7 of the '382 Patent and Claims 20, 34, and 57 of the '444 Patent

102. Orbicular has not proven by clear and convincing evidence that a dosage of 75-80 µg of abaloparatide would have been obvious to a person of ordinary skill in the art as of the priority date of the '382 and '444 patents.

a. Orbicular relies on the combination of Dong 2001 and the Forteo label as teaching a dosage of 75-80 μg of abaloparatide.[12] *See* Karpf Test., Day 1 Tr. at 102-106, 107-113.

   i. Dong 2001 is a two-page abstract reporting the results of three animal studies allegedly demonstrating that abaloparatide is twice as effective as teriparatide.

   ii. Although the maximum dosage of teriparatide approved by the FDA for Forteo is 20 μg, the label for Forteo discloses that a dosage of up to 40 μg of teriparatide was safe and effective during Phase III trials.

b. Orbicular has not shown that a skilled artisan would have reasonably expected from the combination of these references that the optimal abaloparatide dosage would be twice as high as the maximum dosage reported in the Forteo label.

[12] Dr. Karpf relies on the '949 patent only to demonstrate the limitation of using abaloparatide to treat osteoporosis and stimulate bone growth. *See* Karpf Test., Day 1 Tr. at 100-102. Similarly, he relies on WO '775 only to demonstrate the limitation of administering abaloparatide subcutaneously (and to support the seemingly separate concept that the specific change in the abaloparatide sequence from PTHrP would have been obvious). *See id.* at 106-107.

i. Teriparatide is a different peptide than abaloparatide. It is an analog of PTH rather than PTHrP[13] and shares only 40% similarity with abaloparatide in terms of chemical sequence. Trout Test., Day 8 Tr. at 885-886; *see also* Karpf Test., Day 1 Tr. at 58, 73; Forrest Test., Day 3 Tr. at 319-320, 321; Leder Test. Day 6 Tr. at 703.

ii. The court credits the testimony of Dr. Trout that changing even a single amino acid (let alone more than half of the amino acids) in a sequence can significantly alter the properties of the peptide. Trout Test., Day 7 Tr. at 850, 886.

iii. Dong 2001 does not provide any data from the underlying animal studies and was not subjected to the peer review process.[14] *See* Dong 2001; Karpf Test, Day

[13] Dr. Karpf testified that PTHrP was known to have a wider safety margin than PTH. Karpf Test., Day 1 Tr. at 106. But even assuming a skilled artisan would have had a reasonable expectation that abaloparatide could be dosed at higher levels than teriparatide – a proposition contradicted by Dr. Leder, *see* Leder Test., Day 7 Tr. at 743 – that expectation does not lead a skilled artisan inevitably to specific dosage recited in the claims.

[14] The court does not credit Dr. Karpf's suggestion that a skilled artisan would inherently trust the abstract despite the absence of data or a peer review process simply because Dr. Michael Rosenblatt was an author. *See* Karpf Test., Day 1 Tr. at 102-103.

2 Tr. at 180. Given Dr. Karpf's own critique of several aspects of the studies upon which Dong 2001 relies – including its conclusion that the studies demonstrated any twofold potency benefit over teriparatide – when given more information about the studies in 2008, the court does not credit his testimony that a skilled artisan would have reasonably inferred from Dong 2001 that a dose of 80 μg of abaloparatide would be optimal. Trial Ex. AJ.

iv. In one of the underlying studies cited in Dong 2001, the same authors viewed a potential higher potency benefit as paving the way for the administration of *lower* dosages of abaloparatide than teriparatide. *See* Trial Ex. FW. That researchers could reach a conclusion contrary to the one proposed by Orbicular also weighs against any finding that it would have been obvious to a skilled artisan to simply double the maximum dosage disclosed in the Forteo label.

v. Animal studies are not always predictive of what will be observed in humans. Nine in ten drugs fail during Phase

I testing, Leder Test., Day 7 Tr. at 731; *see also* Trial Ex. 48, even though those same drugs had to have been shown to be safe in animal testing to have ever been administered to humans, Karpf Test., Day 1 Tr. at 94.

c. Orbicular has not shown that reaching a dosage of 75-80 µg would otherwise have been a matter of routine optimization.

   i. The court does not credit Dr. Karpf's testimony that a skilled artisan would inevitably reach this dosage during routine optimization. He stated during cross-examination that the dosing regimen for Fosamax, an antiresportive drug which he helped to develop, was inventive despite prior animal testing on the compound and the existence of other antiresorptive drugs on the market. Karpf Test., Day 2 Tr. at 177-178.

d. Because the record does not establish by clear and convincing evidence that the prior art teaches dosing 75-80 µg of abaloparatide, Orbicular has not met its burden of proving that claim 7 of the '382 patent and claims 20, 34, and 57 of the '444 patent are invalid as obvious.

Claim 2 of the ’333 Patent

103. Orbicular has shown by clear and convincing evidence that a storage stable abaloparatide formulation with a pH of 5.1 would have been obvious to a skilled artisan by the priority date of the ’333 patent.

a. Orbicular relies on the combination of the ’949 patent, the ’200 publication, and general knowledge to establish that a skilled artisan would have reasonably expected an abaloparatide formulation to be stable at a pH of 5.1.[15]

i. The ’949 patent discloses the chemical sequence for abaloparatide.

ii. The ’200 publication discloses using a buffer to maintain a preferred pH range of 3 to 6 in formulating Compound I, which shares 33 amino acids in common with abaloparatide.

iii. The court credits the testimony of Dr. Forrest that it was common knowledge by the priority date of the ’333 patent that a pH between 4 and 5 would be ideal to

[15] The motion to strike Dr. Forrest’s testimony on redirect regarding WO ’775 is allowed.

prevent deamidation of glutamine. Forrest Test., Day 3 Tr. at 256, 261-262; *see also* Trial Ex. FR at 437.

iv. The court also credits the testimony of Dr. Forrest that it was common knowledge by the priority date of the patent that isomerization begins to fall at a pH of 5 and is minimized at a pH of 6. Forrest Test., Day 4 Tr. at 360; Trial Ex. FR; *see also* Trout Test., Day 9 Tr. [Dkt # 265] at 1048.

b. Orbicular has shown that a skilled artisan would reasonably expect from the combination of these references that an abaloparatide formulation with a pH of 5.1 would be stable.

i. Abaloparatide contains glutamine and aspartic acid, which a skilled artisan would have viewed as potential hotspots for deamidation and isomerization, respectively.

ii. Dr. Forrest credibly testified that a skilled artisan attempting to balance the potential deamidation and isomerization reactions of abaloparatide would initially target a pH of about 5 in stability testing. *Id.* at 265; *cf.* Trout Test., Day 9 Tr. at 1048-1049.

iii. Dr. Forrest credibly testified that reaching a range of 4.5 to 5.6 (and further narrowing pH down to 5.1) would be a matter of routine optimization from the starting point of a pH of 5. *Id.* at 282-283.

104. Secondary considerations do not compel a finding that the claim is nonobvious.

a. The court credits the testimony of Ms. Shah that Radius has received industry praise for Tymlos and that Tymlos has been a commercial success. Radius has not shown, however, that any praise or commercial success is attributable to Tymlos being stable at a pH of 5.1. At best, it has shown that they are tied to the stability of the formulation *at room temperature* and *without a chemical stabilizer* – neither of which is a limitation of the claim.[16]

b. For similar reasons, Radius has not shown that the stability of an abaloparatide formulation at a pH of 5.1 would have been unexpected. Any surprise attaching to the result is more

[16] The parties previously agreed that a storage-stable formulation is a "composition where the amount, purity of the PTHrP remains above about 95% of the original amount under one of the following conditions: (1) storage for over 2 years at 5° C; ***or*** (2) storage for over 30 days at 25° C." *See* Joint Claim Construction Statement [Dkt # 29-1] (emphasis added).

appropriately attributed to the lack of refrigeration or a chemical stabilizer.

c. The court credits Radius's arguments that the market needed another anabolic treatment for osteoporosis and that Orbicular has been unable, after seven years of trying, to replicate the pH of Tymlos. By themselves, however, the court does not find these factors sufficient to overcome the obviousness of the claim.

105. Because the record establishes by clear and convincing evidence that a storage stable abaloparatide formulation with a pH of 5.1 would have been obvious to a skilled artisan and no secondary considerations compel a contrary conclusion, Orbicular has met its burden of proving that claim 2 of the '333 patent is invalid as obvious.

Claim 11 of the '333 Patent

106. Orbicular has shown by clear and convincing evidence that it would have been obvious by the priority date of the '333 patent to use 5 mg/mL of phenol in the claimed storage stable abaloparatide formulation.

a. Orbicular relies on the combination of the '200 publication and the phenol entry in *The Handbook* to establish that it

would have been obvious to a skilled artisan to use phenol in a dosage of 5 mg/mL in an abaloparatide formulation.

i. The '200 publication discloses using a preservative in a peptide formulation.

ii. *The Handbook* entry provides a high-level overview of phenol.

b. Orbicular has shown that a skilled artisan would reasonably have known to use 5 mg/mL of phenol as a preservative in the claimed abaloparatide formulation.

i. Phenol was a widely used and well known anti-microbial. Forrest Test., Day 3 Tr. at 276, 284; Trial Ex. EM.

ii. Phenol was known to kill many different types of bacteria. Forrest Test., Day 3 Tr. at 276; Trial Ex. EM.

iii. There are only a limited number of preservatives effective in the claimed pH range. Forrest Test., Day 3 Tr. at 283-284; Trial Ex. EM.

iv. Phenol was known to be resistant to (and more effective at) high temperatures.[17] Forrest Test., Day 3 Tr. at 276, 284, 370; Trial Ex. EM.

v. *The Handbook* entry on phenol recommends using a concentration of 0.5% phenol as a preservative in an injection. Trial Ex. EM.

vi. The patent claim is not limited to single use formulations, and Dr. Forrest credibly testified that the FDA requires every product intended for multiuse to include an antimicrobial. Forrest Test., Day 3 Tr. at 274.

107. Secondary considerations do not compel a finding that the claim is nonobvious.

a. For the reasons discussed above, the fact that 5 mg/mL of phenol worked in the claimed abaloparatide formulation was not an unexpected result.

b. Radius has not shown that any industry praise or commercial success is tied to the use of 5 mg/mL of phenol as an antimicrobial.

[17] The preferred preservative in the Forteo patent, m-cresol, requires refrigeration. Forrest Test., Day 4 Tr. at 382.

c. Radius has not shown that any failure to replicate Tymlos on Orbicular's part can be attributed to the use of 5 mg/mL of phenol.

108. Because the record establishes by clear and convincing evidence that a skilled artisan would have reasonably expected success using 5 mg/mL of phenol in the claimed abaloparatide formulation and no secondary considerations compel a contrary conclusion, Orbicular has met its burden of proving that claim 11 of the '333 patent is invalid as obvious.

Claim 13 of the '333 Patent

109. Orbicular has not shown by clear and convincing evidence that a storage stable abaloparatide formulation without a chemical stabilizer would have been obvious to a skilled artisan as of the priority date of the '333 patent.

a. Orbicular relies on the '114 patent to establish that a stable formulation without a chemical stabilizer would have been obvious to a skilled artisan.

i. The '114 patent discloses hundreds of PTHrP analogs.

ii. The '114 patent discloses a generic injectable formulation for a PTHrP analog that does not contain a chemical stabilizer.

b. Orbicular has not shown that a skilled artisan would have reasonably expected from the ’114 patent that an abaloparatide formulation without a chemical stabilizer would be stable.

i. The ’114 patent does not disclose any stability data associated with the recited injectable formulation.

ii. The ’114 patent does not discuss any application of the recited injectable formulation.

iii. The recited injectable formulation is intentionally generic.

1. It does not specify for which of the hundreds of claimed PTHrP analogs should be used.

2. It does not specify what the pH of the formulation should be.

iv. The patent does not mention abaloparatide, and Orbicular has not otherwise shown that abaloparatide is sufficiently similar to the PTHrP analogs disclosed in the ’114 patent that a skilled artisan would reasonably have expected it to behave the same way in a formulation.

110. Because the record does not establish by clear and convincing evidence that a storage stable abaloparatide formulation without a chemical stabilizer would have been obvious to a skilled artisan, Orbicular has not met its burden of proving that claim 13 of the '333 patent is invalid as obvious.

Enablement

111. Orbicular argues that the '208 and '041 patents do not enable a skilled artisan to practice the asserted claims without undue experimentation because they do not disclose how to formulate abaloparatide API with the requisite purity levels.

112. The court credits the testimony of Dr. Penteluete, however, that a skilled artisan would know as a matter of standard practice how to synthesize and/or purify the starting abaloparatide API from existing prior art, without having to practice the "test and toss" method.[18,19] Penteluete Test., Day 10 Tr. at 1113-1114, 1116-1117, 1122-1124, 1129.

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[18] Indeed, abaloparatide is a synthetic analog of PTHrP. As Dr. Penteluete explained, "[I]n reality, a person skilled in the art simply would not devise synthetic methods to make API that did not meet the threshold requirement." Penteluete Test., Day 10 Tr. at 1128.

[19] Orbicular contends that synthesis could not have been routine because the U.S. Patent No. 11,806,387, which post-dates the '208 and '041 patents, is directed to an improved method of synthesizing abaloparatide to reduce impurities. But the '387 patent is directed to reducing a different impurity, des-Gln[16]. The existence of the patent thus does not intimate that minimizing the beta-Asp10 impurity was unknown.

113. In any event, the court agrees with Radius and Ipsen that a skilled artisan could practice the asserted claims without knowing how to formulate abaloparatide API with the requisite purity levels.

114. The claims are directed to a formulated abaloparatide *drug product* – one whose *suitability for administration* has been established by quantifying the presence of beta-Asp10.

115. The specification expressly describes two different methods of assessing the suitability of a formulated drug product for administration by quantifying the presence of beta-Asp10 in a formulated abaloparatide drug product. *See* '208 patent, col. 21, l. 4-col. 27, l. 4.

116. The specification also teaches which storage conditions are needed to minimize isomerization in newly formulated drug product. *See* '208 patent, col. 35, l. 54-58; *id.*, col. 39, l. 9.

117. In sum, Orbicular has not shown by clear and convincing evidence that the asserted claims of the '208 and '041 patents are invalid as not enabled.

Written Description

118. Orbicular makes essentially the same argument with respect to written description that it does with respect to enablement. For the reasons discussed above, it has not shown by clear and convincing evidence that the

asserted claims of the ’208 and ’041 patents are invalid for lack of written description.

ORDER

Consistent with the court’s findings and rulings, the Clerk will enter judgment for Orbicular on claims 2 and 11 of the ’333 patent and for Radius and Ipsen on claim 7 of the ’382 patent; claim 13 of the ’333 patent; claims 20, 34, and 57 of the ’444 patent; claims 14 and 15 of the ’208 patent; and claims 6 and 12 of the ’041 patent.

SO ORDERED.

/s/ Richard G. Stearns
UNITED STATES DISTRICT JUDGE